Docket No.: P0786.70000US05
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	John B. Sullivan et al.
Serial No.:	08/405,454
Confirmation No.:	6004
Filed:	March 15, 1995
For:	ANTIVENOM COMPOSITION CONTAINING FAB FRAGMENTS
Examiner:	Michael P. Woodward
Art Unit:	1637

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Dated: 3/21/11 Signature: /Heather C. McLennand/ (Heather C. McLennand)

SECOND DECLARATION OF RICHARD C. DART, M.D., PH.D.

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Richard C. Dart, hereby declare as follows:

1. I am the same Richard C. Dart who previously submitted a "Declaration of Richard C. Dart, M.D., Ph.D." ("First Dart Declaration") regarding this patent application. [Ex. 1] The facts and opinions contained in the First Dart Declaration remain true.

2. The First Dart Declaration sets forth my credentials as one of ordinary skill in the field of the treatment of snake bite as of October 9, 1984. At that time I was over 3 years into my career as an M.D., including one year at the University of Arizona Health Sciences Center, whose Emergency Room treats as many snake bite victims as any other Emergency Room in the United States.

3. During my Emergency Medicine Residency at the University of Arizona Health Sciences Center, Tucson, AZ, I developed a strong interest in the treatment of various poisonings, especially

snake venom poisoning. As of October 9, 1984, I was also preparing to start my Fellowship in Clinical Toxicology at the University of Arizona Health Sciences Center where snake venom poisoning was a major toxicological issue.

4. As of October 9, 1984, I understood as one of ordinary skill in the art when snake bite treatment might be effective and what potential side effects might be seen, as well as the molecular mechanisms and biological interactions involved. Indeed, my status as one of ordinary skill in developing treatments for snake venom poisoning soon thereafter allowed me to obtain my first grant regarding potential improvements to rattlesnake antivenom in 1985 [Ex. 2 at p. 42], based on a grant application I began preparing in mid-1984. And I was invited by an out-of-state institution (California Medical Center Hospital) to update their staff on developments in treatments of snake venom poisoning also in 1985. [Ex. 2 at p. 35]

5. I understand that the US Patent and Trademark Office ("PTO") has again rejected the claims of this patent application based on the Fab fragment teachings of the Coulter et al. article [Ex. 3] and the affinity-purified antibody teachings of the Sullivan et al. article [Ex. 4] but on a diffcrent ground than before. Now, the USPTO bases its rejection on the belief that:

> It would have been obvious to a person having ordinary skill in the art at the time the invention was made to have prepared Fab fragments from either purified IgG or $F(ab)_2$ preparations and to have included them with such preparations to obtain an antivenom which would neutralize venom at its depot sites as well as in the blood stream.

[Ex. 5 at p. 42.]

6. I disagree that one of ordinary skill in the art would have had any reason to make Fab fragments from either purified IgG or $F(ab)_2$ preparations and to have included them with such preparations. As explained in the First Dart Declaration, one of ordinary skill in the art would not have extrapolated from the Coulter et al. article's report of the ability of Fab fragments raised to the textilotoxin component of *Psuedonaja textilis* venom to neutralize the lethality of that single component of *Psuedonaja textilis* venom to the ability of Fab fragments to neutralize:

1) *Psuedonaja textilis* venom as a whole by administering Fab fragments raised to just textilotoxin;

2) *Psuedonaja textilis* venom as a whole by administering Fab fragments raised to the entire venom; or

3) *Crotalus* venom as a whole by administering Fab fragments raised to *Crotalus* venom.

[Ex. 1 at ¶¶ 20-28.] Accordingly, one of ordinary skill in the art would not have found it obvious to have used Fab fragments in an antivenom, either alone or in combination with IgG or $F(ab)_2$ fragments.

7. The PTO disagreed with my views, asserting that the complexity of venoms "does not lead to the conclusion that the Coulter et al. results cannot be extended to venom per se." [Ex. 5 at p. 42.] As explained in detail in the First Dart Declaration, I do not agree that one of ordinary skill in the art would have extrapolated from a) the lethality neutralizing ability of Fab fragments to **a single toxin** of *Psuedonaja textilis* venom to b) the lethality neutralizing ability of Fab fragments to **the entire venom** of *Psuedonaja textilis*. All the lethal toxins of a venom must be neutralized in order to neutralize the lethality of the venom. [Ex. 1 at ¶ 23.]

8. Indeed, a commercial antivenom that neutralizes textilotoxin—the very *Psuedonaja textilis* venom toxin neutralized by Fab fragments in the Coulter et al. article—sometimes fails to neutralize the lethality of *Psuedonaja textilis* venom because it does not neutralize other lethal toxins of *Psuedonaja textilis* venom. [Ex. 1 at ¶ 24.] Again, snake venoms contain an arsenal of lethal toxins, whose only commonality is being contained in the same venom. The ability to neutralize a single lethal toxin component of this arsenal would not allow one of ordinary skill in the art to extrapolate to neutralizing all the otherwise unrelated lethal toxin components of this arsenal.

9. I cannot determine why the PTO rejected my views and this evidence supporting them. The PTO simply asserted that "complexity does not lead to the conclusion that the Coulter et al. results cannot be extended to venom per se." [Ex. 5 at p. 42; see also p. 13.] For the reasons discussed above and in the First Dart Declaration, I disagree that one of ordinary skill in the art would have

extended Coulter et al.'s results with a single toxin to venom per se, which would require Fab fragments to neutralize the lethality of each and every lethal component of the venom.

10. As further evidence that the PTO's views of what one of ordinary skill in the art would have extrapolated from the Coulter et al. article are incorrect, I have attached a citation search report for it. [Ex. 6] The Coulter et al. article has received a fair amount of attention in the literature, with 61 articles citing it. But not one of those 61 articles cited the Coulter et al. article for the antivenom teachings the PTO says can be extrapolated from it. Only the PTO has made this extrapolation from the Coulter et al. article.

11. The PTO based its new rejection on the different pharmacokinetic properties of a) Fab fragments and b) $F(ab)_2$ fragments and IgG, in relation to those of venom toxins, making the following statements:

> However, the smaller Fab fragments should exhibit more rapid tissue infiltration, and ameliorate the local effects of the venom. This raises the interesting question of whether or not an anti-venom comprised of either IgGs or F(ab)2 in combination with Fabs would be more effective than either IgG or F(ab)2 alone.
>
> [Ex. 5 at p. 20.]
>
> Each declarant was aware of the depot effects of venom and the local tissue damage which resulted, each further recognized that Fabs could reach such sites yet each chose to emphasize the drawbacks of rapid elimination of Fabs from the circulatory system. The person of ordinary skill in the art at the time the invention was made was aware of the local and systemic effects of envenomation, and was equally aware that intravenous administration of antivenom was frequently an effective treatment.
>
> [Ex. 5 at p. 41.]
>
> It would have been obvious to a person having ordinary skill in the art at the time the invention was made to have prepared Fab fragments from either purified IgG or $F(ab)_2$ preparations and to have included them with such preparations to obtain an antivenom which would neutralize venom at its depot sites as well as in the blood stream.

[Ex. 5 at p. 42.]

One of ordinary skill in the art at the time the invention was made would have found it obvious to have modified the commercially available Bothrops antivenoms to preparations containing Fabs with the expectation that such inclusion would result in a more effective antivenom preparation.

[Ex. 5 at p. 43.]

12. One of ordinary skill in the art simply would not have believed as of October 9, 1984 that Fabs fragments could be added to existing IgG or $F(ab)_2$ preparations to obtain a beneficial additive effect. As evidence of this, the following real-world experience demonstrates that, even with a specific motivation to prepare a combined Fab and $F(ab)_2$ preparation, those of ordinary skill in the art took many years to arrive at that potential solution.

13. The first clinical trial of CroFab identified a recurrence issue. [Ex. 7.] After an initial response, three patients demonstrated recurrent symptoms. [Ex. 7 at p. 37, col. 1.] This was an important finding, and we speculated on several potential causes of this recurrence, two of which related to the short-half life of Fab fragments, and the first of which specifically concerned the venom depot effect. [Ex. 7 at pp. 37-38.]

14. Given the importance of the recurrence findings, a major aim of the second (phase 3) CroFab clinical trial was to investigate whether maintenance doses would address the postulated mismatch between the half-lives of Fab fragments and venom toxins. [Ex. 8.] After initial control of symptoms, patients were administered subsequent doses of CroFab either as needed or according to a maintenance dosing schedule. Half of the as-needed patients exhibited recurrence and required additional doses, and none of the maintenance patients required additional doses. [Ex. 8 at p. 2034, col. 2.] Again, we speculated as to causes of the recurrence, with the short half-life of Fab fragments figuring prominently, particularly the venom depot effect. [Ex. 8 at pp. 2034-35.]

15. We also published a case report for a patient from the as-needed group of the phase 3 trial. [Ex. 9.] The patient required 2 additional vials of CroFab to treat recurrence on 3 different

occasions. We subsequently measured both the levels of venom antigens and the level of unbound Fab fragments in samples of the patient's blood. We found that the recurrence coincided with a return of detectable venom antigens, which had been undetectable following initial treatment, and a decrease in Fab fragments. [Ex. 9 at 51, col. 1.] Again, we speculated that the recurrence was due to the short-half life of Fab fragments and the venom-depot effect. [Ex. 9 at p. 51 ("we postulate that a depot of unneutralized venom formed at the bite site and caused the recurrence of local symptoms once circulating free Fab antivenom decreased below a protective concentration."]

16. We conducted a detailed analysis of the recurrence results from the two clinical trials. [Ex. 10.] Over half the patients (53%) exhibited late, persistent, or recurrent coagulopathy. [Ex. 10 at p. 708. col. 2.] We concluded that the short half-life of Fab fragments, particularly in conjuction with the venom depot effect, was likely responsible for the recurrence. [Ex. 10 at pp. 709-10.] And we suggested close monitoring of patients for 2 weeks after envenomation. [Ex. 10 at p. 710.]

17. The issue of recurrence was of such importance that those in the field analyzed it even in studies designed for other purposes. Thus, an article published concerning the use of CroFab to treat copperhead snake (*Agkistrodon*) envenomation assessed recurrence. [Ex. 11.] Six of 32 patients treated developed recurrence, and additional treatment with CroFab was effective in all but 1 of those 6 patients. [Ex. 11 at p. 204.]

18. Several other articles also observed and discussed the issue of recurrence. [Exs. 12-16] Generally, the literature noted that recurrence could occur even when maintenance doses were given, and that patients needed to by monitored, especially those that exhibited coagulopathy, which was the most important recurrent symptom.

19. The issue of recurrence with CroFab was so important that one group even published a two-part series on recurrence. [Ex. 17; Ex. 18.] This series included guidelines for clinical management of recurrence and also recommended post-treatment follow-up, and upon recurrence, treatment with repeated doses and "at least daily" follow-up. [Ex. 18 at p. 200.]

20. The companion article discussed additional improvements in CroFab's dosing and composition that might address the recurrence problem. Thus, intramuscular injection, improved purification, alteration of charge or complexation with glycosate or dextran, and coadministration of other substances that block renal accumulation of Fab fragments were all suggested as potential improvements to address the apparent mismatch between rapid clearance of Fab fragments and late release of venom toxins. [Ex. 17.]

21. Thus, at least six years of published articles by several different groups discussed the issue of recurrence, postulated that it was due to the short half-life of Fab fragments and the venom depot effect, and considered ways to avoid or treat the venom depot effect, including structural alterations to the Fab fragments and the coadministration of other compounds to alter the pharmacokinetics of the Fab fragments. Despite all this attention to CroFab's recurrence issue and the venom depot effect, the first publication that I am aware of that suggested addressing the recurrence exhibited by CroFab by combining Fab and $F(ab)_2$ fragments in an antivenom was not published until 2003. [Ex. 19.]

22. Gutierrez et al. discussed the CroFab recurrence issue that was discussed in Exhibits 8, 10, 17, and 18, attributing it to the short half-life of Fab fragments resulting in reduced levels of Fab fragments in the blood when late venom release from tissues occured. [Ex. 19 at p. 736.] Gutierrez et al. went on to conclude that:

> The complexity of venoms, many of which include both LMM [low molecular weight] and HMM [high molecular weight] toxins having different targets and mechanisms of action, makes the selection of the ideal pharmacokinetic profile of an antivenom a rather difficult and controversial task. Owing to this complexity, **some antivenoms may have to include a mixture of Fab fragments and IgG or $F(ab')_2$ molecules**. The former, having rapid equilibration and large volume of distribution, would allow rapid neutralisation of small toxins in tissues, whereas the latter would assure repeated cycling in tissues and high plasma levels for a relatively extended time.

[Ex. 19 at p. 737 (emphasis added).]

23. Gutierrez et al. reached this conclusion in 2003 based on the same reasoning the PTO asserted would have motivated one of ordinary skill in the art in 1984 to have combined Fab fragments from an existing $F(ab)_2$ or IgG antivenom with such an antivenom. Fab fragments "would allow rapid neutralisation of small toxins in tissues" according to Gutierrez et al. [Ex. 19 at p. 737] or "neutralize venom at its depot sites" [Ex. 5 at p. 42, p. 20 ("ameliorate the local effects of venom")] according to the PTO. The $F(ab)_2$ fragments "would assure repeated cycling in tissues and high plasma levels for a relatively extended time" according to Gutierrez et al. [Ex. 19 at p. 737] or "neutralize venom . . . in the blood stream" according to the PTO. [Ex. 5 at p. 42.]

24. However, when the field of antivenom development was presented with the very real-world problem of CroFab's recurrence issue, which generated an extensive body of literature, it took the field over 6 years of intense study for anyone to suggest combining Fab fragments with $F(ab)_2$ fragments or IgG in an antivenom. In light of that fact, I simply cannot agree with the PTO that one of ordinary skill in the art would have concluded from the Sullivan et al. and Coulter et al. articles that it would have been obvious to combine Fab fragments with an existing $F(ab)_2$ or IgG antivenom "to obtain an antivenom which would neutralize venom at its depot sites as well as in the blood stream." [Ex. 5 at p. 42.] As of October 9, 1984, it would not have been obvious to a person having ordinary skill in the art to prepare antivenoms comprised of Fab fragments and either IgG or $F(ab)_2$ fragments.

25. I also cannot agree that one of ordinary skill in the art would have derived from the Sullivan et al. and Coulter et al. articles a concern about the need to somehow treat both the immediate, local effects of venom toxins and their delayed, systemic effects differently. The apparent pharmacokinetic mismatch between Fab fragments and some venom toxins was not even discussed until many years later. Even if such a motivation existed in 1984, however, I cannot agree that the purported motivation would have made it obvious to combine Fab fragments with an existing $F(ab)_2$ or IgG antivenom to address it. Again, it took the field **over 6 years** of intense study to first suggest this idea, and that was only when presented with the real-world problem of recurrence, and **almost 20 years after October 8, 1984.**

26. For all the above reasons, in addition to those set forth in the First Dart Declaration, at the time the patent application was filed on October 9, 1984, it would not have been obvious for one of ordinary skill in the art to prepare an antivenom comprised of Fab fragments and either $F(ab)_2$ fragments or IgG.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: 3/18/11

Richard C. Dart, M.D., Ph.D.